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EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,457	NAKAMURA ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's response filed 01/15/2009 is acknowledged. Claims 1-11 have been cancelled and replaced with new claims 12-18. Therefore, all rejections made in the previous Office action mailed 09/15/2008 are withdrawn as moot, and any rejections set forth in this Office action are new rejections necessitated by Applicant's amendment.

Response to Arguments

Applicant's arguments filed 01/15/2009 have been considered but are moot in view of the new ground(s) of rejection. As regards Applicant's description on page 7 of the response:

> Therefore, the number of base-pairs to be formed between the target nucleic acid probe and the target nucleic acid and the GC contents of the probe (i.e. the GC contents of the nucleic acid) will be equal to that between the target nucleic acid probe and the internal standard nucleic acid and the GC content of the nucleic acid or the internal standard nucleic acid.
>
> As a result, there will be no substantial difference in heat stability between the hybridized complex to be formed by the target nucleic acid probe and the target nucleic acid and that to be formed by the internal standard nucleic acid probe and the target nucleic acid. Therefore, the probes are both considered to hybridize likewise with the target nucleic acid and the internal standard nucleic acid without distinguishing from each other.

It is respectfully submitted that these features are not recited in the claim. Although the claims are interpreted in light of the specification, limitations from

the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim/Specification Objections

The use of the trademarks PACIFIC BLUE® and ECLIPSE QUENCHER™ have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

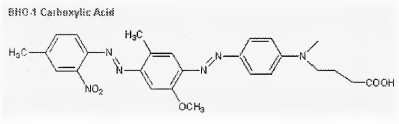
The following is a quotation of the second paragraph of 35 U.S.C. 112:

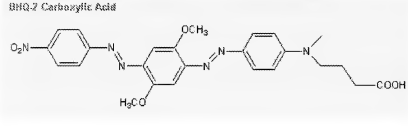
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

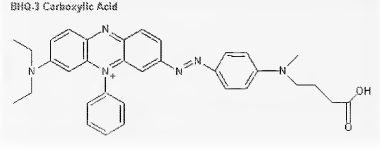
Claims 12, 13 and 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 13, 15, and 17 contain the trademark/trade name BODIPY® FL. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and

not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a fluorescent dye (4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-propionic acid) and, accordingly, the identification/description is indefinite. Similarly, PACIFIC BLUE® (1,2-ditetradecanoyl-sn-glycero-3-phosphoethanolamine) is a trademark. Similarly, ECLIPSE QUENCHER™ in claim 18 is a trademark. Similarly BHQ (BLACK HOLE QUENCHER™) in claim 18 is a trademark, and moreover there are multiple types of BHQ:







Applicant is advised to recite the chemical names of these compounds in the claims.

Claim 16 recites "...when the target nucleic acid contains, on an outer side of a base sequence of said portion thereof, guanine at neither a second base nor a third base as counted from a first base as counted from a first base paired with a base at the other one of the 5'-end and 3'-end of the target nucleic probe (A)...". It is unclear what the other one refers to here. Is this the end other than the one labeled with a fluorescent dye? Or is it the end other than the one labeled with a quencher? Or is it the end other than the one having a cytosine? Also, with regard to the last option, it is noted that "has a cytosine as a base at one of the 5'-end and 3'-end" leaves open the possibility that both ends of the probe have cytosine as the terminal base, in which case the last option would make no sense. For purposes of examination over the prior art, the examiner will assume, based on figure 13 of the application, that the probe is intended to have cytosine as a terminal base at only one of the 5' or 3' ends of the probe, and that "the other one of the 5'-end and 3'-end" refers to the "non-C" end.

Nevertheless, appropriate clarification is required. As claims 17 and 18 depend from claim 16, they are rejected for the same reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Kurata et al (Nucleic Acids Research 29(6):e34 (5 pages) 2001, cited on the IDS of 06/19/2006) as evidenced by:

GenBank GI:223462484 [online] Feb 11, 2009 [retrieved on Apr 8, 2009] retrieved from http://www.ncbi.nlm.nih.gov/nuccore/223462484, and

GenBank GI:211581525 [online] Nov 1, 2008 [retrieved on Apr 8, 2009] retrieved from http://www.ncbi.nlm.nih.gov/nuccore/211581525 (as this document is extremely large, only the first page has been supplied with this Office action).

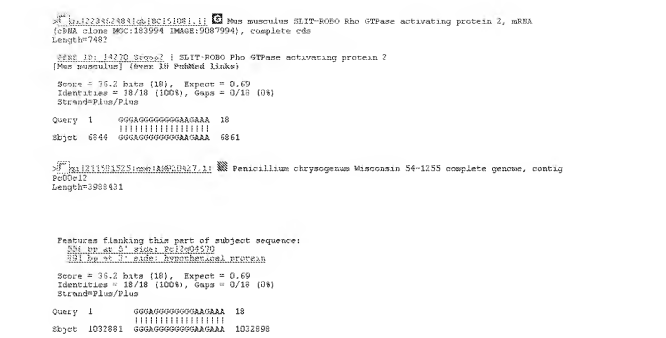
Claim 12 is a mixture requiring only two components: a target nucleic acid probe and an internal standard nucleic acid. No target is required to be present in the mixture, and no particular target nucleic acid is recited in the claim. Therefore, the structure of the target nucleic acid probe and the internal standard are not limited by any particular target sequence.

Kurata teaches a number of mixtures in which an oligonucleotide labeled at the 5' end with BODIPY FL was hybridized to a complementary nucleic acid sequence. The labeled oligonucleotide meets the limitations of the target nucleic acid probe (since the claims are not limited to any particular target nucleic acid sequence) and the complementary nucleic acid sequence meets the limitations of the internal standard (again, as the claims are not limited to any particular target nucleic acid sequence). For example, in Table 1, teaches the combination of 5'-CCCCCCCCCTTTTTT-3' (the labeled oligonucleotide, i.e. the "target nucleic acid probe") and 5'-GGGGGGGGGGGGAAAAAA-3' (the complementary oligonucleotide; i.e. the "internal standard nucleic acid"). Note that according to

Table 1, the fluorescence of the BODIPY-FL label is quenched 92% upon hybridization of the two strands. Claim 12 recites that "the internal standard nucleic acid (B) has a base sequence portion that is the same as the base sequence of the portion of the at least one target nucleic acid except that one of a first to third base as counted from the first base, which can be paired with the fluorescence-labeled base of the nucleic acid probe (A), and another base in the base sequence of the portion of the at least one target nucleic acid have been replaced with each other and one of the replaced bases is guanine".

However, the mixture taught by Kurata anticipates the claimed mixture because: (1) the claims are not limited to any particular nucleic acid target, (2) the claimed mixture is not required to comprise the actual target nucleic acid and therefore (3) the target nucleic acid to which the claim refers need not be disclosed in the prior art (only the mixture comprising the target nucleic acid probe and the internal standard nucleic acid need be disclosed in the prior art to preclude patentability). Hence, a target comprising the sequence 5'-GGGAGGGGGGGGAAGAAA-3' is a nucleic acid target (note the underlined positions represent the bases "replaced with each other" relative to the internal standard nucleic acid, which is Kurata's 5'-GGGGGGGGGGGGAAAAAA-3'; note also that the underlined "A" is the "first base" as set forth in the claim).

Now, it so happens that this "target" is found in at least two organisms (*Mus musculus* and *Penicillium chrysogenum*):



However, it is asserted that even if this "target" were *not* found in a naturally occurring sequence (or even in the prior art), but was instead merely an arbitrary exchange of relevant bases in Kurata's sequence 5'-GGGGGGGGGGGGAAAAAA-3' generated by the examiner (which, in fact, was the case here, and by chance the resulting sequence *also* happened to be a naturally occurring sequence), Kurata still anticipates for the same reason (i.e. it is only the mixture of a labeled probe and an internal standard that must be disclosed by the prior art).

If the claim were allowed, all one would need to do to demonstrate the invalidity of the claim would be to disclose a "target" sequence such as the examiner has done above. There could be no argument that Kurata's mixture does not anticipate, because there would be absolutely nothing different about Kurata's mixture before or after the later disclosure of such a "target". For this

reason, although the examiner has relied on the GenBank sequences in an evidentiary manner, the rejection would still be valid even if such "target" sequences had never been disclosed.

Claims 12 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Tremmel et al (Tissue Antigens 54:508-516, 1999) as evidenced by:

(i) Belousov et al (US 2003/0175728)

(ii) GenBank GI:5174458 [online] Jun 24, 1999 [retrieved on Apr 8, 2009] retrieved from:

http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?5174458:OLD02:500876

(iii) GenBank GI:170522971 [online] Mar 25, 2008 [retrieved on Apr 8, 2009] retrieved from:

http://www.ncbi.nlm.nih.gov/nuccore/170522971.

With regard to claims 12, 14 and 15, Tremmel taught a TaqMan PCR assay wherein a probe labeled at the 5' and 3' ends with different fluorescent dyes was included in a PCR mixture along with genomic DNA comprising a sequence with which the probes were designed to hybridize (see figure 1, page 509 and "Amplification", pages 510-511). Hence, this PCR mixture comprises a probe as recited in claims 12, 14 and 15, and an "internal standard" which can be met by the genomic DNA and/or the PCR product which is produced during the reaction.

For example, in Table 4, page 512, Tremmel discloses a "probe 3" which is labeled at the 5' end with TET and at the 3' end with TAMRA. As each of these dyes is recited by claims 12 and 15, it is asserted that these dyes can be quenched by interacting with guanine. This probe 3 was used as a control for amplification; it was designed to hybridize to a non-polymorphic region of exon 2 of the HLA-DMA gene (see page 511, section entitled "Internal amplification control").

The claimed "internal standard" is met by the genomic DNA included in the mixture. Tremmel clearly states that the TET-labeled probe (probe 3) in Table 4 was used to detect the amplicon from the non-polymorphic region of exon 2 of the HLA-DMA gene (see page 511, section entitled "Internal amplification control"). As evidence that the HLA-DMA gene does in fact comprise a sequence hybridizable to Tremmel's probe 3, the examiner relies on GenBank GI:5174458 which discloses the sequence of the HLA-DMA gene ("Query" is Tremmel's probe sequence, "Sbjct" is a portion of the GenBank sequence, with position numbers indicated):

```
Query  1    TCGCCTGCCCGAATTTGCTGA  21
           ||||||||||||||||||||
Sbjct  285  TCGCCTGCCCGAATTTGCTGA  305
```

Therefore, when Tremmel combined probe 3 and genomic DNA in the PCR reaction mixture, he inherently made and taught how to make the claimed mixture. That is to say, human genomic DNA, which is double-stranded, inherently comprises the sequence 5'-TCAGCAAATTCGGGCAGGCGA-3' (the

complementary strand of the GenBank sequence portion shown above). This is the claimed "internal standard".

This satisfies the limitations of claims 12, 14 and 15. Claims 12 and 14 recite that "the internal standard nucleic acid (B) has a base sequence portion that is the same as the base sequence of the portion of the at least one target nucleic acid except that one of a first to third base as counted from the first base, which can be paired with the fluorescence-labeled base of the nucleic acid probe (A), and another base in the base sequence of the portion of the at least one target nucleic acid have been replaced with each other and one of the replaced bases is guanine".

However, the mixture taught by Tremmel anticipates the claimed mixture because: (1) the claims are not limited to any particular nucleic acid target, (2) the claimed mixture is not required to comprise the actual target nucleic acid and therefore (3) the target nucleic acid to which the claim refers need not be disclosed in the prior art (only the mixture comprising the target nucleic acid probe and the internal standard nucleic acid need be disclosed in the prior art to preclude patentability).

Hence, a sequence comprising 5'-TCAGCAAATTCGGGCGGGCAA-3' is a nucleic acid target (note the underlined positions represent the bases "replaced with each other" relative to the internal standard nucleic acid, which is the sequence 5'-TCAGCAAATTCGGGCAGGCGA-3' inherently present in the genomic DNA in Tremmel's mixture. Note that the underlined "A" is the "second base" counted from the 3' terminal base (i.e. the "first base") which hybridizes to

the 5' terminal base of probe 3 (which is labeled with TET; see Tremmel Table 4). For the same reasoning as discussed in the rejection over Kurata et al above, it is not necessary that the "target sequence" 5'-TCAGCAAATTCGGGCGGGCAA-3' be disclosed in the prior art, since nothing would change about Tremmel's mixture whether or not said "target sequence" was disclosed.

Claim 16 is not met by the mixture comprising probe 3 and genomic DNA, but rather by the mixture comprising probe 1 (see Tremmel Table 4) and genomic DNA from the HLA-DRB1*15 positive volunteers (see page 509, "DNA samples"). This is because claim 16 requires that the claimed nucleic acid probe has a cytosine as a base at one of the 5' or 3' end. Tremmel's probe 1 comprises cytosine at the 3' end. In addition, probe 1 is labeled at the 5' end with FAM and at the 3' end with TAMRA (which is a quencher; see "Principle of the TaqMan method", page 509: "...a quencher dye (TAMRA)..."). As evidenced by the footnote of Belousov Table 2 (page 23), FAM can be quenched by interaction with guanine.

As evidenced by GenBank GI:170522971, human genomic DNA from the HLA-DRB1*15 positive volunteers (see page 509, "DNA samples") comprises a sequence hybridizable to probe 1 ("Query" is Tremmel's probe sequence, "Sbjct" is a portion of the GenBank sequence, with position numbers indicated):

```
>gi|170522971|gb|EU523128.1| Homo sapiens MHC class II antigen (HLA-DRB1) gene, HLA-DRB1*15
variant allele, exon 2 and partial cds
Length=270

 Score = 42.1 bits (21),  Expect = 0.017
 Identities = 21/21 (100%), Gaps = 0/21 (0%)
 Strand=Plus/Plus

Query  1    TCCGTGCGCTTCGACAGCGAC  21
            |||||||||||||||||||||
Sbjct  96   TCCGTGCGCTTCGACAGCGAC  116
```

Therefore, when Tremmel combined probe 3 and genomic DNA from the HLA-DRB1*15 positive volunteers in the PCR reaction mixture, he inherently made and taught how to make the claimed mixture. That is to say, genomic DNA from the HLA-DRB1*15 positive volunteers, which is double-stranded, inherently comprises the sequence 5'-GTCGCTGTCGAAGCGCACGGA-3' (the complementary strand of the GenBank sequence portion shown above). This is the claimed "internal standard". Note that this sequence has a guanine (at the 5' end) that can pair with the cytosine at the 3' end of Tremmel's probe 1.

Claim 16 also recites:

when the target nucleic acid contains, on an outer side of a base sequence of said portion thereof, guanine at neither a second base nor a third base as counted from a first base paired with a base at the other one of the 5'-end and 3'-end of the target nucleic probe (A), the internal standard nucleic acid (B) contains guanine as at least one of the second and third bases on an outer side of said base sequence, and

when the at least one target nucleic acid contains, on said outer side of the base sequence of the portion, guanine as at least one of the second and third bases, the internal standard nucleic acid (B) contains guanine as neither the second base nor the third base on the outer side of the base sequence

As far as the examiner can reason (see rejection under 35 U.S.C. 112, 2nd paragraph), what is intended by this language is the following: when the target (not required in the claimed mixture) and the probe are hybridized, counting the base in the target opposite the "non-C" terminal nucleotide as position 1, if

neither of positions 2 or 3 (on the "outside") are guanine, then the internal standard comprises guanine at one of these positions. If the target comprises guanine at either of these positions, then the internal standard does not have guanine at either of these positions. However, since no specific target is recited by the claim, these limitations do not distinguish over Tremmel's mixture. The basis of the rejection is that the genomic DNA from the HLA-DRB1*15 positive volunteers is the "internal standard". Based on the GenBank GI:170522971 sequence, the genomic DNA from the HLA-DRB1*15 positive volunteers would have a T and C, respectively, at the 2nd and 3rd "outside positions" when hybridized to Tremmel's probe 1 (where the CT corresponds to the reverse complement of positions 94-95 of GenBank GI:170522971):

Hence, a target comprising the sequence 3'-CGAGGCACGCGAAGCTGTCGCTG-5' is a nucleic acid target. For the same reasoning as discussed in the rejection over Kurata et al above, it is not necessary that this "target sequence" be disclosed in the prior art, since nothing would change about Tremmel's mixture whether or not said "target sequence" was disclosed.

Claims 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (Genome Research 8:549-556 (1998)).

With regard to claim 12, Chen taught a mixture comprising sample DNA, primers and probes for detection of single nucleotide polymorphisms (see abstract and figure 1). In the mixture, a single 5' labeled probe (labeled with FAM) is designed to hybridize adjacent to one of two 3' labeled probes (labeled with either ROX or TAMRA). In a particular working example, Chen performed the assay (thus generating a mixture) for the C/T β°-thalassemia mutation (see figure 2). The relevant probes included in this mixture are shown in Table 1 (THAL-A, -B and -C). Since Chen actually made a mixture comprising genomic DNA from an individual comprising the T allele (corresponding to the 3' TAMRA labeled THAL-C probe; see figure 2 and Table 1), he inherently produced a mixture comprising said genomic DNA (which can be considered the claimed "internal standard") and the THAL-C probe (which can be considered the claimed probe). Because the THAL-C and THAL-A probes were designed to hybridize adjacently (see figure 1) to genomic DNA from a T^+ individual, it can be concluded that the genomic DNA from these individuals (e.g. lanes 1 and 2, figure 2) comprised genomic DNA having the sequence 5'-GACTCAAAGAACCTCTA*GGTCCAAGGGTAGA-3' (the reverse complementary sequence of the THAL-C and THAL-A probes; the * indicating the junction between the probes). This genomic DNA then represents the claimed internal standard.

Hence, a sequence comprising 5'-AACTCGAAGAACCTCTA*GGTCCAAGGGTAGA-3' is a nucleic acid target (note the underlined positions represent the bases "replaced with each other"

relative to the internal standard nucleic acid, which is the sequence 5'-GACTCAAAGAACCTCTA*GGTCCAAGGGTAGA-3' inherently present in the genomic DNA in Chen's mixtures used to produce the reactions shown in lanes 1 and 2 of figure 2. Note that the underlined "A" is the "first base" counted from the which hybridizes to the 3' terminal base of probe THAL-C (which is labeled with TAMRA; see Table 1). For the same reasoning as discussed in the rejection over Kurata et al above, it is not necessary that the "target sequence" 5'-AACTCGAAGAACCTCTA*GGTCCAAGGGTAGA-3' be disclosed in the prior art, since nothing would change about Chen's mixture whether or not said "target sequence" was disclosed.

With regard to claim 13, note that Chen's mixture also comprised a second probe (THAL-A), which was labeled with FAM (see Table 1). Claim 13 does not recite that the labels for *each* of the two probes are selected from those recited in claim 12, or that *each* of the two different fluorescent labels are quenchable by guanine (although FAM, in fact, is quenchable by guanine). Also note that each of Chen's two probes comprises a base sequence that hybridizes to "a portion" of the base sequence of a target nucleic acid (and, consequently, the internal standard). Although claim 13 recites "probes each of which has *the base sequence* hybridizable with *the portion* of the at least one target", one can consider *the portion* of the target as being 5'-AACTCGAAGAACCTCTA*GGTCCAAGGGTAGA-3' (and consider *the portion* of the internal standard as being 5'-GACTCAAAGAACCTCTA*GGTCCAAGGGTAGA-3'). One can also consider

the base sequence as referring generically to *a base sequence hybridizable with a portion of the base sequence of the at least one target* as recited in claim 12. Claim 13 does not require that *the base sequence* of the first probe is the same as *the base sequence* of the second probe.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tremmel et al (Tissue Antigens 54:508-516, 1999) as evidenced by:

(i) Belousov et al (US 2003/0175728)

(ii) GenBank GI:5174458 [online] Jun 24, 1999 [retrieved on Apr 8, 2009] retrieved from:

http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?5174458:OLD02:500876

(iii) GenBank GI:170522971 [online] Mar 25, 2008 [retrieved on Apr 8, 2009] retrieved from:

http://www.ncbi.nlm.nih.gov/nuccore/170522971.

The teachings of Tremmel, Belousov, GenBank GI:5174458 and 170522971 have been discussed.

As discussed above, the only probe in Tremmel's disclosure that comprised cytosine at either of the 5' or 3' ends (as required by claim 16) was probe 1 (see Table 4). However, while this probe was labeled with TAMRA (one of the recited options of claim 17), the language of claim 16 clearly implies that one end of the probe is labeled with a fluorescent dye, and the other end is labeled with a quencher. Therefore, the TAMRA on probe 1 cannot simultaneously fulfill the limitation as to the fluorescent dye on one end of the probe and the quencher on the other. The examiner has taken the position that TAMRA is the quencher and FAM is the fluorescent dye.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to exchange the FAM labels used for probes 1 and 2 with the TET label used for probe 3. As is clear from Tremmel's disclosure, both FAM and TET were suitable fluorescent dyes for use in FRET with the quencher TAMRA (see figure 1 and paragraph spanning pages 509-510). It is *prima facie* obvious to substitute equivalents known for the same

purpose (MPEP 2144.06). By simply exchanging the fluorescent dyes between the typing probes (probes 1 and 2) and the control probe (probe 3), one would have arrived at the invention of claim 17, since probe 1 would then comprise TET as the fluorescent dye and TAMRA as the quencher.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tremmel et al (Tissue Antigens 54:508-516, 1999) as evidenced by:

(i) Belousov et al (US 2003/0175728)

(ii) GenBank GI:5174458 [online] Jun 24, 1999 [retrieved on Apr 8, 2009] retrieved from:

http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?5174458:OLD02:500876

(iii) GenBank GI:170522971 [online] Mar 25, 2008 [retrieved on Apr 8, 2009] retrieved from:

http://www.ncbi.nlm.nih.gov/nuccore/170522971

and further in view of Belousov et al (US 2003/0175728).

Note that this rejection relies on Belousov in both an evidentiary and prior art manner.

The teachings of Tremmel, Belousov, GenBank GI:5174458 and 170522971 have been discussed. None of Tremmel's probes comprised as quenchers those elements recited in claim 18.

Belousov discloses a number of "preferred quenchers" (paragraph [0114]), including TAMRA (used by Tremmel), DABCYL and BHQ (Black Hole™ Quenchers BH-1, BH-2 and BH-3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute TAMRA with DABCYL or BHQ as the quencher on Tremmel's probes since Belousov clearly taught all these compounds as equivalents for use as quenching moieties to be used in conjunction with fluorescently labeled nucleic acid probes (MPEP 2144.06). In making such substitution, one would have arrived at the mixture of claim 18.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone

number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637

/Young J Kim/
Primary Examiner, Art Unit 1637